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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,265	11/04/2003	Brenda F. Baker	ISIS-5300	7033

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
04/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	10/701,265	BAKER ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *120,121,124,127 and 136-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *120, 121, 124, 127, and 136-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed December 14, 2010.

Claim 120 has been amended.

Claims 120, 121, 124, 127, and 136-138 are pending in the instant application.

Claims 120, 121, 124, 127, and 136-138 have been examined on the merits as detailed below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed July 14, 2010, claims 120, 121, 124, 127, and 136-138 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 14, 2010.

It is noted that claim 120 has been amended to recite, "The second chemically synthesized oligonucleotide comprises at least one nucleoside that comprises a 2'-sugar modification". At the time the invention was made, those in the art routinely synthesized oligonucleotides comprising at least one nucleoside that comprises a 2'-

sugar modification. See, for example, Monia et al. and Shibahara et al. Therefore, claims 121, 124, 127, 136-138, and claim 120 as now amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989).

Response to Arguments

In response to this rejection, Applicants argue that those of ordinary skill in the art would have had no reason to design and produce the claimed oligomeric compounds at the time of invention. Specifically, Applicants contend that those of ordinary skill in the art would not have had a reason at the time of invention to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modiffied wings and the second oligonucleotide comprises at least one 2'-sugar modification, in view of the description provided in the references. Applicants then go one to discuss the Wyatt article, the Manche article, the Monia article, and the Shibahara application.

Applicant is reminded that the test for obviousness is not whether the features of the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *See In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck* & Co., Inc., 800 F.2d 1091, 231 USPQ 375.

Additionally, Applicant argues against the Wyatt article, the Manche article, the Monia article, and the Shibahara application individually, but must consider the rejection based upon the combination of the references. See MPEP 2145. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck* & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding Wyatt, Applicants contend that nothing about the design or nature of the experiments described in the Wyatt article would have provided a reason to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex. This contention has been fully considered, but is not found persuasive because the prior art taught the desire to introduce sugar-modified nucleosides into nucleic acid molecules for the purpose of protecting the oligonucleotide from exonucleases, increasing stability of the nucleic acid and enhancing target specificity and affinity. See Shibahara et al., and Monia et al., for example. Contrary to Applicant's contention, one of ordinary skill in the art would have been motivated to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex because, based on the prior art, such duplexes would be resistant to various nucleases and increase stability of the oligonucleotide.

Regarding Manche, Applicants argue that nothing about the nature or aim of the experiments described in the Manche article provides any reason that would have prompted those of ordinary skill in the art to produce chemically modified RNA duplexes, much less duplexes having at least one sugar-modified nucleoside in both

strands. This argument has been fully considered, but is not found persuasive. Regarding the production of chemically modified RNA duplexes, Wyatt et al., for example, teach duplexes of complementary 14-mer oligoribonucleotides in which 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy and ribo-nucleotides.

Regarding duplexes having at least one sugar-modified nucleoside in both strands, as noted above, the prior art taught the desire to introduce sugar-modified nucleosides into nucleic acid molecules for the purpose of protecting the oligonucleotide from exonucleases, increasing stability of the nucleic acid and enhancing target specificity and affinity. See Shibahara et al., and Monia et al., for example. Therefore, and contrary to Applicant's contention, one of ordinary skill in the art would have been motivated to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex because, based on the prior art, such duplexes would be resistant to various nucleases and increase stability of the oligonucleotide.

Regarding Monia, Applicants argue that the Monia article contains no teaching or description that would have prompted those of ordinary skill in the art to incorporate at least one modified sugar into both strands of an oligomeric compound duplex. Furthermore, Applicants contend that in experiments in which the antisense activity of single-stranded gapmers was analyzed, duplexes were not introduced into HeLa cells, but rather single-stranded gapmers were introduced, and their activity against unmodified, full-length mRNA target was determined. Applicants assert that accordingly, nothing about the design or objective of the experiments described in the

Monia article would have prompted those of ordinary skill in the art to incorporate chemical modifications into both strands of an oligonucleotide duplex, much less incorporate 2'-modified wings into the first oligonucleotide and at least 2'-sugar modifications into the second oligonucleotide. Applicant's arguments, contentions, and assertions have been fully considered, but are not found persuasive because first it should be noted that Monia et al. teach duplexes comprising first and second chemically synthesized 17-25-nucleotide long oligonucleotides, wherein the first oligonucleotide is 100% complementary to the second oligonucleotide. Monia et al. also teach that the first oligonucleotide is a 17-mer gapmer having phosphorothioate linkages, at least 4 deoxyribonucleosides (DNA) in the gap, and each wing comprises 2'-OMe-modified nucleotides. The second oligonucleotide is a 25-mer synthetic oligoribonucleotide (RNA) that is a portion of Ha-ras mRNA. The first oligonucleotide has 100% complementarity to Ha-ras and to the second oligonucleotide.

Furthermore, Monia et al. teach that:

> "Chimeric 2'-modified/deoxy phosphorothioates displayed greater anti-sense potencies in inhibiting Ha-*ras* gene expression when compared with the unmodified uniform deoxy phosphorothioate." See Abstract.

Moreover, Monia et al. explicitly teach:

> "Affinity of an oligonucleotide for its target RNA can be increased substantially by incorporation of 2'-O-methyl modifications, with relative affinity being directly proportional to 2'-O-methyl content". See page 14518, first column.

Therefore, given these teachings, it is the Examiner's position that the combination Wyatt et al., Manche et al., Monia et al., and the Shibahara application

would have directed one ordinary skill in the art to incorporate at least one modified sugar into both strands of an oligomeric compound duplex.

Regarding Shibahara, Applicants argue that the Shibahara application describes single-stranded antisense ribooligonucleotides. Applicants contend that although the Shibahara application describes chemical modification of antisense ribooligonucleotides, including 2'-OMe modifications, the Shibahara application does not describe or suggest any reason to introduce chemical modifications into oligonucleotide duplexes. These arguments and contentions have been fully considered but are not found persuasive because the combination of the prior art renders the instant application obvious over Wyatt article, the Manche article, the Monia article, and the Shibahara application. This is primarily due to the fact that Wyatt et al. teach duplexes of complementary 14-mer oligoribonucleotides in which 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy and ribo-nucleotides. Manche et al. teach the desire to make short RNA duplexes. Monia et al. teach duplexes comprising first and second chemically synthesized 17-25-nucleotide long oligonucleotides, wherein the first oligonucleotide is 100% complementary to the second oligonucleotide. Furthermore, Monia et al. explicitly teach that the affinity of an oligonucleotide for its target RNA can be increased substantially by incorporation of 2'-O-methyl modifications. Similarly, the Shibahara application teaches chemically modified oligonucleotides.

Therefore, using the combined teachings of Wyatt article, the Manche article, the Monia article, and the Shibahara application, it would have been *prima facie* obvious for

one of ordinary skill in the art to introduce 2'-sugar modifications into both strands of an oligonucleotide duplex.

Applicants lastly argue that the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation could have occurred. Applicants contend that the cited references fail to provide any reason that would have prompted those of ordinary skill in the art to protect both strands of an oligonucleotide duplex of the length claimed against nucleolytic degradation by introducing chemical modifications into both strands of such duplexes. Applicants further argue that such duplexes of Applicant's claimed invention would not have been particularly suitable for the research described in the references.

Applicant's arguments have been fully considered, but are not fond persuasive because in addition to providing protection against nuclease degradation, chemical modification of oligonucleotides also has the added benefit of increasing stability of the nucleic acid and enhancing target specificity and affinity. See Monia et al., for example. Furthermore, Monia et al. discuss the use of modified nucleic acids for oligonucleotide therapeutic purposes. Therefore, one of ordinary skill in the art would have the desire to modify oligonucleotides for use in an environment in which undesired nucleolytic degradation occurs.

Moreover, it is acknowledged that the prior art references taught experiments in which single-stranded nucleic acids were introduced into cells. However, one of ordinary skill in the art would have substituted the single-stranded nucleic acids of the prior art with the double-stranded nucleic acid duplexes of Applicant's claimed invention

because KSR forecloses that the simple substitution of one known element for another would have yielded predictable results at the time of the invention. See recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385). Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

In view of the foregoing, when all the evidence is considered, the totality of the rebuttal evidence of non-obviousness fails to outweigh the evidence of obviousness made of record. Thus, it is maintained that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Double Patenting

In the previous Office Action mailed July 14, 2010, claims 120, 121, 124, 127, and 136-138 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 130-156 of copending Application No. **10/859825** in view of Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 14, 2010.

In the previous Office Action mailed July 14, 2010, claims 120, 121, 124, 127, and 136-138 were provisionally rejected on the ground of nonstatutory obviousness-

type double patenting as being unpatentable over claims 86-123 of copending Application No. **10/701264** in view of Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 14, 2010.

Response to Arguments

In response to these rejections, Applicants request that the rejections be deferred pending the identification of allowable subject matter in the present application. The Examiner acknowledges Applicant's response. It is noted that the double patenting rejections will be held in abeyance pending indication of allowance subject matter in the instant application.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamite can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

April 5, 2011
/Terra Cotta Gibbs/

/Sean R McGarry/
Primary Examiner, Art Unit 1635